NTP Research Concept: Aminopyridines

Project Leader
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Nomination Background and Rationale
The National Cancer Institute (NCI) nominated aminopyridines[20] (APs) for study because of the lack of information suitable to predict chronic toxicity for this class chemicals, and an interest in conducting structure/activity studies. There are three APs under consideration for this nomination:

2-Aminopyridine (2-AP, 504-29-0) is used as an intermediate in the manufacturing of pharmaceuticals, and has a reported U. S. production of 10,000-500,000 pounds per year from 1986-2002 (except in 1998 when production climbed to 1,000,000-10,000,000 pounds). 3-Aminopyridine (3-AP, 462-08-8) is used as an intermediate in the production of pharmaceuticals, agrochemicals and dyes. 4-Aminopyridine (4-AP, 504-24-5), a registered pesticide, is under development as a drug to treat multiple sclerosis and other neurological diseases. Acordia Therapeutics received approval for clinical trials of Fampridine (4-AP) for treatment of multiple sclerosis (MS) in 2007 (http://phx.corporate-ir.net/phoenix.zhtml?c=194451&p=irol-newsArticle&ID=1037327&highlight). The proposed mechanism for 4-AP treatment of MS is prolongation of nerve action potential. No U. S. production figures are available for 3-AP or 4-AP.

There are no standard toxicity studies for the aminopyridines reported in the literature. Under the nomination, NCI requested: toxicological characterization of 2-, 3- and 4-AP including a 2-year cancer study of 2-AP; short-term mechanistic studies of 2-, 3- and 4-AP; and neurotoxicity evaluation of 2-, 3- and 4-AP. Toxicological testing of 2-AP was considered to be of relatively higher priority because of the higher production volume and potential occupational exposure.

Aminopyridines block K^+ channels in isolated nerve preparations and myocytes, and, thus, the heart and neurologic system are potential AP target organs[3,4,13,16,18,22,24]. 4-AP is considered the most potent K^+ channel blocker followed by 3-AP and 2-AP. NTP studies of pyridine and chloropyridine identified chemical-induced liver toxicity, and, thus, liver toxicity may also occur after AP exposure due to similarities in pyridine and substituted pyridine metabolism patterns. Aminopyridines alter lymphocyte activation[12] and cause apoptosis[5], and therefore immunologic toxicity may also be a possible side effect from AP exposures.

Key issues
- Use of toxicity tests to detect heart, liver, neurologic, or immunologic toxicity
- Relationship between rodent toxicity endpoints and blood levels of aminopyridine to levels of aminopyridines reported to block K^+ channels

Proposed Research Program

Hypotheses

- Aminopyridines will cause neurotoxicity, cardiac toxicity and/or immunotoxicity at exposure levels that block K^+ channels.

- Aminopyridines will cause liver toxicity at exposures levels comparable to pyridine exposures that cause liver toxicity.

Specific Aims

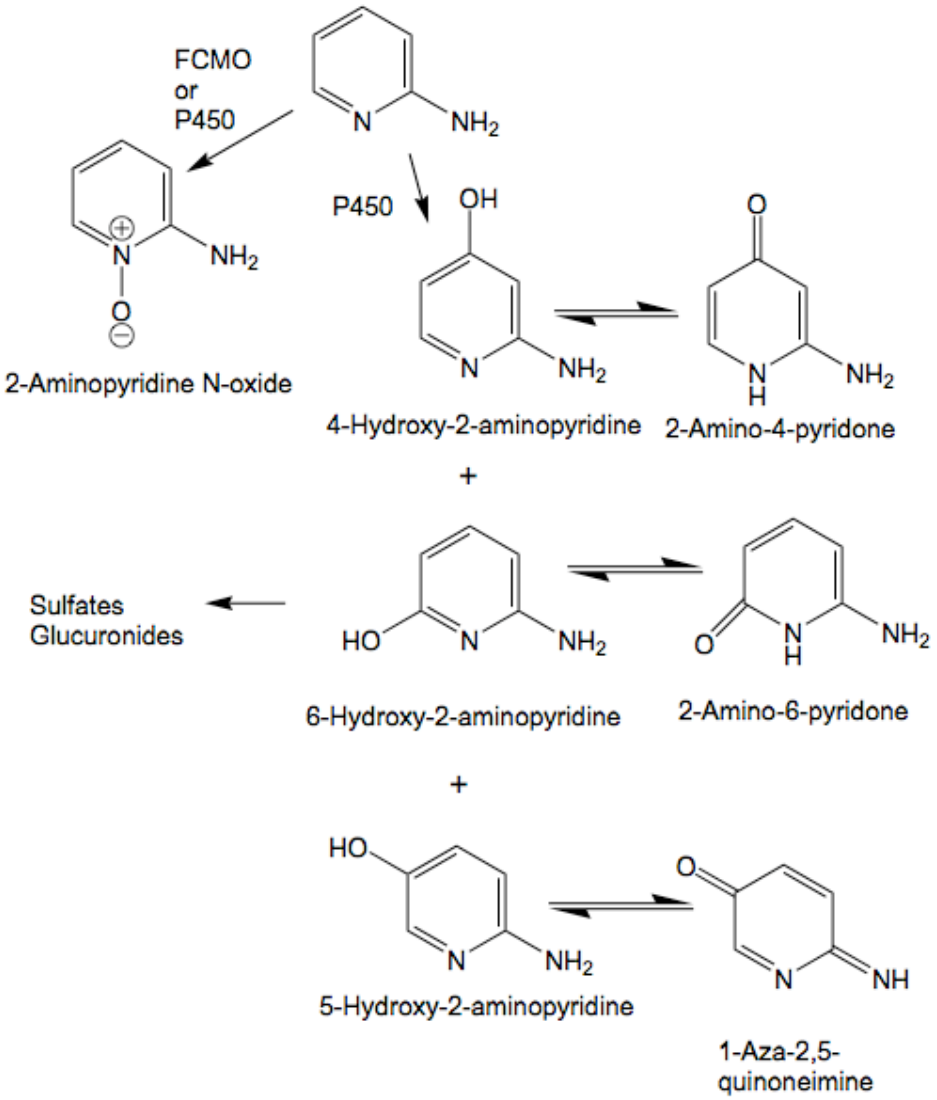
Toxicity studies designed to identify neurotoxicity, cardiotoxicity (including serum troponin levels or alterations in EKGs [10,14,15]), liver toxicity, or immunotoxicity are proposed since they would help to elucidate relative toxicities of the different APs. In vitro electrophysiology studies will also be considered to analyze potential neurotoxicity. The results from these toxicity studies will be used to identify the need for chronic carcinogenicity studies or further AP mechanistic studies.

Aminopyridine metabolism/toxicokinetic studies are proposed, as they would provide information for comparing rodent AP serum levels with AP serum levels found in humans. The aminopyridines are expected to be oxidized by cytochromes P450 or flavin-containing monoxygenases yielding hydroxylated aminopyridines and aminopyridine N-oxides (see attached proposed metabolism)[19].

Evaluation of changes in gene transcript levels have been used to provide a "fingerprint" of target organ toxicity (e. g. heart[1,6,7,21] or liver[2,11,17,23]), and such studies will be considered to understand AP toxicity pathways. Comparative genotoxicity tests and high throughput tests (HTT) (e. g. ion channel HTTs) may be used to provide additional comparative toxicity information for this class of chemicals.

Significance and Expected Outcomes

This project will provide hazard identification information for 2-, 3-, and 4-aminopyridine, and provide comparative toxicity information for the aminopyridine class.


FCMO
or
P450
2-Aminopyridine N-oxide
P450
4-Hydroxy-2-aminopyridine
2-Amino-4-pyridone
+
Sulfates
Glucuronides
6-Hydroxy-2-aminopyridine
2-Amino-6-pyridone
+
5-Hydroxy-2-aminopyridine
1-Aza-2,5-
quinoneimine

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